

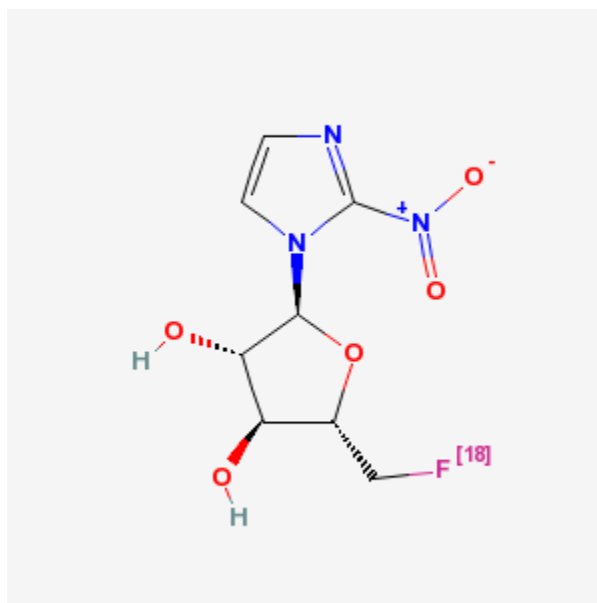
1-(5- $[^{18}\text{F}]$ Fluoro-5-deoxy- α -D-arabinofuranosyl)-2-nitroimidazole

$[^{18}\text{F}]$ FAZA

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Chemical name:	1-(5- $[^{18}\text{F}]$ Fluoro-5-deoxy- α -D-arabinofuranosyl)-2-nitroimidazole
Abbreviated name:	$[^{18}\text{F}]$ FAZA
Synonym:	$[^{18}\text{F}]$ Fluoroazomycinarabinofuranoside, $[^{18}\text{F}]$ Fluoroazomycin arabinoside
Backbone:	Compound
Target:	Hypoxic tissue
Mechanism:	Intracellular reduction and binding to macromolecules
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
In vitro studies:	Yes
Rodent studies:	Yes
Other non-primate mammal studies:	No
Non-human primate studies:	No
Human studies:	No



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Background

[PubMed]

Hypoxia is found in a variety of solid tumors, leading to tumor progression and the resistance of the tumors to chemotherapy and radiotherapy (1-3). Tumor oxygenation is heterogeneously distributed within human tumors (4). It would be beneficial to assess tumor oxygenation before and after therapy to provide an evaluation of tumor response to treatment and an insight into new therapeutic treatments (5). Tumor oxygenation is measured invasively using computerized polarographic oxygen-sensitive electrodes, which is regarded as the gold standard (6). Functional and non-invasive imaging of intratumoral hypoxia has been demonstrated to be feasible for the measurement of tumor oxygenation (7).

Chapman (8) proposed the use of 2-nitroimidazoles for hypoxia imaging in 1979. 2-Nitroimidazole compounds are postulated to undergo reduction in hypoxic conditions, forming highly reactive oxygen radicals that subsequently bind covalently to macromolecules inside the cells (9). [¹⁸F]Fluoromisonidazole ([¹⁸F]FMISO) is the most widely used positron emission tomography (PET) tracer for imaging tumor hypoxia (7). However, it has slow clearance kinetics and a high lipophilicity, resulting in substantially high background in PET scans. [¹⁸F]Fluoroazomycin-arabinofuranoside ([¹⁸F]FAZA) is a 2-nitroimidazole with a sugar addition (10). [¹⁸F]FAZA has been studied as a hypoxia imaging agent, showing promising results in various tumor models in rats and mice (11, 12).

Synthesis

[PubMed]

[¹⁸F]FAZA was readily synthesized by standard nucleophilic substitution conditions (Kryptofix 2.2.2 and K₂CO₃), followed by hydrolysis of the protective acetyl groups using 1-(2,3-di-*O*-acetyl-5-*O*-tosyl- α -D-arabinofuranosyl)-2-nitroimidazole and [¹⁸F]fluoride (12). Radiochemical yield averaged 20% (decay corrected), based on [¹⁸F]fluoride, and the specific activity averaged 2 GBq/ μ mol (54 mCi/ μ mol) at the end of synthesis. Radiochemical and chemical purities were 90-95%, as determined by high-performance liquid chromatography (HPLC). Reisch et al. (10) used an automated synthesis to provide an overall radiochemical yield of $20.7 \pm 3.5\%$ (not decay corrected) and absolute yields up to 9.8 ± 2.3 GBq (260 ± 62 mCi) at the end of synthesis. The synthesis time was 50 min.

In comparison studies, [¹⁸F]FMISO was synthesized using 1-(2-nitro-1-imidazolyl)-2-*O*-tetrahydropyranyl-3-*O*-toluene-sulfonylpropane-diol by nucleophilic substitution with [¹⁸F]fluoride, followed by hydrolysis (12). This provided [¹⁸F]FMISO in 80% (decay corrected) radiochemical yield and 90-95% radiochemical purity at the end of synthesis, with a specific activity of 2 GBq/ μ mol (54 mCi/ μ mol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro studies (12) indicated that uptake of both [¹⁸F]FAZA and [¹⁸F]FMISO in Walker 256 rat tumor cells in hypoxic culture condition ($pO_2 < 3$ mm Hg) in 20 and 100 min of incubation was of the same magnitude (20 min: $1.24 \pm 0.4\%$ ([¹⁸F]FAZA); $1.19 \pm 0.7\%$ ([¹⁸F]FMISO); 100 min: $3.6 \pm 1.6\%$ ([¹⁸F]FAZA); $3.3 \pm 1.7\%$ ([¹⁸F]FMISO)). Under normoxic culture condition (pO_2 , 70 mm Hg), their uptake was similar but lower than in the hypoxic condition (20 min: $0.9 \pm 0.4\%$ ([¹⁸F]FAZA); $0.74 \pm 0.3\%$ ([¹⁸F]FMISO); 100 min: $1.1 \pm 0.6\%$ ([¹⁸F]FAZA); $1.4 \pm 0.6\%$ ([¹⁸F]FMISO)).

Animal Studies

Rodents

[PubMed]

Standardized uptake values (SUVs, Bq per cm^3 X body weight in g divided by injected dose) for $[^{18}\text{F}]$ FAZA and $[^{18}\text{F}]$ FMISO were determined with PET scans in rats bearing Walker 256 carcinosarcomas in their right hind legs (12). Tissue $p\text{O}_2$ values of the normal muscle and tumors were 50-70 and <5 mm Hg, respectively. One h after tracer injection, the SUVs in tumors were 0.68 ± 0.2 for $[^{18}\text{F}]$ FAZA and 1.07 ± 0.3 for $[^{18}\text{F}]$ FMISO ($p < 0.05$). Corresponding SUVs in muscle tissue were 0.29 ± 0.09 for $[^{18}\text{F}]$ FAZA and 0.40 ± 0.09 for $[^{18}\text{F}]$ FMISO ($p < 0.05$). The concentration of $[^{18}\text{F}]$ FAZA in tumor and muscle tissue at 3 h after tracer injection was concordantly decreased to SUVs of 0.35 ± 0.12 (tumor) and 0.13 ± 0.05 (muscle). However, the SUV for $[^{18}\text{F}]$ FMISO in the tumor tissue remained unchanged in 3-h PET imaging (1.11 ± 0.7), although it was lower in comparison with early PET scans for the muscle tissue (0.26 ± 0.15). Tumor-to-muscle SUV ratio was not significantly different ($[^{18}\text{F}]$ FAZA, 2.4 ± 0.6 ; $[^{18}\text{F}]$ FMISO, 2.7 ± 0.6) when measured 1 h after injection. However, the tumor-to-muscle ratio was significantly higher for $[^{18}\text{F}]$ FMISO in comparison with $[^{18}\text{F}]$ FAZA (4.4 ± 1.3 versus 2.9 ± 0.6 , $p < 0.05$) at 3 h. PET images showed that $[^{18}\text{F}]$ FAZA radioactivity was eliminated via the renal system with high radioactivity in the kidneys and urinary bladder and low radioactivity in the liver. In contrast, $[^{18}\text{F}]$ FMISO was high in the kidneys and liver. $[^{18}\text{F}]$ FAZA showed a faster clearance from the body than $[^{18}\text{F}]$ FMISO, providing a lower background than $[^{18}\text{F}]$ FMISO.

Biodistribution studies (11) of $[^{18}\text{F}]$ FAZA in nude mice bearing AR42J tumors show a rapid clearance of the tracer from the body over time (10, 60, and 180 min after injection). The highest decrease in radioactivity was found in the blood, and the lowest decrease was found in tumor and brain. The tumor-to-muscle ratio increased with time. $[^{18}\text{F}]$ FAZA was eliminated via renal excretion and hepatic metabolism as the radioactivity in the liver and kidneys also decreased from 10 to 180 min. The highest radioactivity was found in the urine (100% injected dose (ID)/g urine), followed by the tumor, intestines, kidneys, and liver at 180 min.

$[^{18}\text{F}]$ FAZA and $[^{18}\text{F}]$ FMISO biodistribution studies were compared in the three different tumor models (EMT6 BALB/c mice, AR42J and A431 Swiss nude mice) at 3 h after tracer injection (11). $[^{18}\text{F}]$ FAZA exhibited a significantly lower uptake in most organs, including the liver and kidneys, and a much faster clearance from the blood compared with $[^{18}\text{F}]$ FMISO. In contrast, tumor uptake was not significantly different between both tracers in two of the three tumor models studied. However, $[^{18}\text{F}]$ FAZA showed a more favorable tumor-to-blood ratio and tumor-to-organ ratios than $[^{18}\text{F}]$ FMISO. Tumor hypoxia was assessed in EMT6 ($p\text{O}_2$, 2.9 ± 2.6) and AR42J ($p\text{O}_2$, 0.4 ± 0.2) by oxygen electrode measurements as compared with normal tissue ($p\text{O}_2$, 25.8-29.0). Therefore, tumor uptake of $[^{18}\text{F}]$ FAZA correlates inversely with oxygen concentration.

Serial animal $[^{18}\text{F}]$ FAZA PET studies (11) were performed in nude mice bearing A431 tumors and showed that the tumor-to-background ratio was significantly higher in mice breathing room air compared with that of mice breathing pure oxygen (7.3 ± 2.3 versus 4.2 ± 1.2 , respectively; $p <$

0.001). Similarly, autoradiography studies in mice bearing EMT6 tumors showed significantly higher tumor-to-muscle ratios in mice breathing room air compared with those of animals breathing carbogen (95% O₂ and 5% CO₂) (5.3 ± 0.8 versus 2.2 ± 0.8 ; respectively; $p < 0.02$). Hence, uptake of [¹⁸F]FAZA would be decreased by improving tumor tissue oxygenation through therapy.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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